Nitric Oxide is Involved in Cardiac Resistance to Ischemic Injury in Calorically Restricted Mice

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Caloric restriction (CR) exerts a variety of health benefits in mammals including protection against ischemic damage in the heart. Adiponectin, an adipokine that increases under starvation and senses the cellular energy status, has been implicated in cardioprotection induced by CR. Factors such as pAMPK, eNOS (endothelial Nitric Oxide Synthase) and STAT3 have been previously linked to adiponectin-induced cardioprotection. CR-induced cardiprotection has been studied so far in ex vivo and in vitro models for cardiac ischemic stress, but rarely in in vivo models. Here we studied this issue after ligation in vivo of left descending (LAD) coronary artery. We compared C57Bl mice fed 65% of their normal food intake for 2 weeks to control mice fed ad libitum. Cardiac functions were tested and blood and tissue samples were taken before and 24 hours after ligation.

The results demonstrated that CR significantly improved left ventricular functions. CR also reduced infarct size, inflammatory cytokines, the number of neutrophils and apoptotic cells and levels of caspase 3 and pJun, suggesting the involvement of both inflammation and apoptosis in the damage to the cardiac tissue. CR also significantly increased (45%) the levels of adiponectin in the serum of non-treated CR mice. In addition, phosphorylation of AMPK, eNOS, STAT3, and AKT as well as the levels of VEGF were higher in the ischemic heart of CR mice. The difference in cardiac functions between LAD-treated CR and control mice was abrogated after pretreatment with L-NAME, an inhibitor of NO formation by NOS.

These results show that short-term CR can confer resistance against ischemic damage in the heart using, for the first time, an in vivo model for myocardial infarction. Adiponectin and several signaling factors correlated with this resistance. The finding that L-NAME could abrogate the improvement in ventricular functions indicates that NO is involved in CR-induced cardioprotection.